Impact of Intracellular Signaling in Colorectal Cancer (CRC)

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Colorectal cancer (CRC) is one of the leading causes of cancer death worldwide. The development of local and/or distant tumor recurrences after completed anti-cancer therapy is a major problem in the treatment of CRC. The problem of CRC recurrences should be discovered in details in order to propose predictive biomarkers and improve therapy results in CRC patients. A growing body of evidence supports an idea that development of CRC recurrences may be closely associated with therapy-resistant carcinoma stem cells. According to the hypothesis of carcinoma stem cells (also referred to as tumor-initiating cells), malignant tumors contain a fraction of cells possessing the abilities for self-renewal and generation of heterogeneous lineages of cancer cells comprising the tumor [1,2]. Therefore, it is logical to suggest that the malignant tumor could be cured only when all cancer stem cells will be killed. In order to improve treatment outcome in patients with recurrent and/or metastatic CRC (mCRC), the reliable biomarkers and targets to detect and destroy CRC stem cells are urgently needed. Nowadays, various targeting therapeutics are used in combination with conventional therapy approaches. It is generally believed that targeted compounds could effectively kill tumor cells, because they are directed against products of genes possessing causative link with tumorigenesis. However, the existing targeted therapeutics reveal very limited clinical benefit in mCRC patients [3]. It is possible to suggest that the low response rate and disappointed clinical benefit might be related to the ineffective killing of CRC stem cells, whereas the majority population of non-stem cells are effectively destroyed upon treatment using targeted compounds.

Inhibition of Epidermal Growth Factor Receptors (EGFR) became a standard mCRC therapy and is widely combined with chemotherapeutics and radiation therapy [3,4]. However, the clinical response rate in the overall mCRC patient population is limited to approximately 10% [5-7]. Perhaps carcinoma stem cells reveal any specific intracellular signaling properties protecting cells from the potentially active anti-EGFR compounds. It is already known that EGFR inhibitors do not demonstrate anti-tumor efficacy when carcinoma cells possess KRAS mutations. Therefore, the European Medical Agency (EMEA) restricted the use of EGFR blockers only to mCRC patients with wild type KRAS. Response rate to anti-EGFR therapy in mCRC patients with wild type KRAS is approximately 40-60% [8,9]. Perhaps even wild type RAS might be activated in carcinoma cells resulting in hyperactivity of EGFR-related pathway and insensitivity to EGFR blockers. Therefore, the following questions are raised: (1) whether RAS status can contribute to the aggressiveness of CRC stem cells; (2) which upstream and downstream pathways are associated with RAS activation; (3) which biomarkers could be used to predict activation of RAS pathway resulting in the reduced sensitivity to EGFR blockers; (4) which novel targeted compounds could enhance an anti-tumor activity of anti-EGFR agents in mCRC patients with activated RAS pathway.

Hyperactivity of EGFR-related pathway due to the enhanced activity of RAS may contribute to the formation of highly aggressive carcinoma cells with increased metastatic activity [10,11]. It has become apparent that EGFR-RAS-MAPK pathway triggers Snail and Slug transcription factors [8]. Both of them are known to repress E-cadherin that results in induction of epithelial-mesenchymal transition (EMT) [8]. It was already reported, malignant tumors with activated EMT program demonstrate the reduced sensitivity to anti-EGFR agents [8,12]. Clinical trials are urgently needed to prove whether concomitant RAS activation and initiation of EMT program may be considered biomarkers of CRC resistance to EGFR blockers.

It has been recently proposed that EMT may provide a link between highly metastatic phenotype, tumor aggressiveness, lower sensitivity to anticancer therapy and generation of carcinoma stem cells [11]. Recent studies have demonstrated that EMT induction in epithelial tumor cells can lead to the generation of cells possessing stem cell properties, such as lower proliferative rate, self renewal and chemoresistance [13-15]. Since activation of RAS-related pathways could lead to initiation of EMT and cancer stem cell formation, it is logical to suggest that activation of other members of RAS superfamily may trigger generation of carcinoma stem cells. Thus, the Rho family is a subgroup of the RAS superfamily of small GTPases. One of the best-characterized members of Rho GTPases is Rac1 protein. Rac1 is an intracellular molecule participating in the regulation of various oncogenic pathways. Increased expression and/or enhanced activity of Rac1 protein have been found in a variety of malignant tumors including CRC [16,17]. Rac1 is one of the major regulators of cell cycle and proliferation, membrane raffling, lamellipodia formation, cell motility and migration [18,19]. Similar to activation of RAS-related signalling, Rac1 overexpression is associated with initiation of EMT [19]. It was additionally shown that Rac1 overexpression is implicated in the development of cancer cell resistance to anti-ErbB2 monoclonal antibody trastuzumab [20]. It was demonstrated that Rac1 triggering consists with affected SAPK/JNK and ERK signalling in carcinoma cells [20]. Perhaps, CRCs revealing activated RAS also show resistance to EGFR blockers due to up-regulated activity of Rac1 protein and Rac1-related pathways.

In summary, the problem of local and/or distant CRC recurrences may be associated with triggering of various intracellular signaling events related to activation of RAS pathway. This activation can lead to the formation of highly aggressive, therapy resistant carcinoma stem cells inclining to metastatic spread. Detailed investigation of the currently unknown protein networks that are involved in the regulation of the well known pathways (for example, EGFR-related pathway) could provide oncologists with novel putative biomarkers to predict tumor response to therapeutic agents and targets to improve CRC therapy results.

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